Support for these amendments can be found throughout the specification. Applicant notes that adequate description under the first paragraph of 35 U.S.C. §112 does not require literal support for the claimed invention. Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an appellant had possession of the concept of what is claimed. Support for "wherein each n-mer is at least 8 nucleotides in length" is found, for example, at Page 11, Lines 15-20, at Page 13, Lines 3-11, at Page 17, Lines 19-30 and the Examples. Support for "microarray" is found, for example, at Page 19, Lines 4-8; Page 23, Lines 3-5; Page 29, Lines 25-27; Page 32, Lines 11-12. Applicant submits that these amendments do not constitute new matter.

§103 Rejection of the Claims

Claims 1-18 were rejected under 35 USC § 103(a) as allegedly unpatentable over Cantor et al. (U.S. Patent No. 5,631,134, filed June 5, 1995) in view of Southern (U.S.Patent No. 5,700,637, filed April 19, 1994). According to the Examiner, the '134 patent teaches the claimed subject matter of the present application. The Examiner cites the '134 patent at column 8, lines 1-12; column 4, lines 5-8 and column 12, lines 9-19 as evidence of these alleged teachings.

Applicant respectfully submits that the present claims are not prima facie obvious over the cited references. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings so as to arrive at the claimed invention. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest all of the claim limitations. The teachings or suggestions, as well as the expectation of success, must come from the prior art, not applicant's disclosure.

The claims are directed to the use of microarrays having complete sets of n-mers where each n-mer is at least 8 nucleotides in length. Neither of the cited references discloses or teaches such microarrays. Therefore, the cited references do not teach or suggest all of the claim limitations as required for obviousness. Moreover, the teachings of the cited references do not provide a reasonable expectation of successfully practicing the invention.

In particular, claim 1 is directed to a method of determining the presence of a mutation in a target polynucleotide without sequencing the target polynucleotide. The steps of the method of claim 1 include (a) providing at least two identical polynucleotide probe microarrays, wherein each probe comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in each microarray constitute a complete set of n-mers, wherein each n-mer is at least 8 nucleotides in length; (b) hybridizing the target polynucleotide to said overhangs of probe polynucleotides in one microarray to generate a target hybridization pattern; (c) hybridizing a reference polynucleotide to said overhangs of probe polynucleotides in a second microarray to generate a reference hybridization pattern; and (d) determining the presence of a mutation in the target polynucleotide by comparing the reference and target hybridization patterns without sequencing the target polynucleotide.

Claim 12 is directed to a method of determining whether two or more target polynucleotides are identical without sequencing the target polynucleotides. Step (a) of claim 12 is the same as step (a) of claim 1. Step (b) of claim 12 involves hybridizing first target polynucleotide to said overhangs of probe polynucleotides in one microarray to generate a first hybridization pattern. Step (c) of claim 12 involves hybridizing second target polynucleotide to said overhangs of probe polynucleotides in a second microarray to generate a second hybridization pattern. Step (d) of claim 12 involves comparing the first and second hybridization patterns.

Applicant submits that the '134 patent does not provide a reasonable expectation of successfully practicing the invention and actually teaches away from the use of a microarray with a complete set of n-mers, where the n-mer is 8 nucleotides or longer. For example, the '134 patent teaches as follows:

> [T]here are still a number of potentially severe drawbacks to actual sequencing by hybridization. First and foremost among these is that 4^n rapidly becomes quite a large number if chemical synthesis of all of the oligonucleotide probes is actually contemplated.

'134 Patent, col. 2, lines 37-42.

> [F]ar fewer than all probes are necessary to determine reliable sequence data. . .

'134 Patent, col. 2, lines 33-34.

> However, to determine the complete sequence of a nucleic acid target, the set of probes need not contain every possible combination of nucleotides of the random sequence to be encompassed by the method of this invention. . . For a nucleic acid sequence of length k, there are $4(2^k-1)$ instead of 4^k probes. Where k = 8, a set of probes would consist of only 1020 different members instead of the entire set of 65,536. The savings in time and expense would be considerable.

'134 Patent, col. 6, lines 6-17. Accordingly, the '134 patent teaches that there are severe drawbacks to using a complete set of n-mers, that not all n-mers are needed, and that there would be considerable savings in time and expense when using less than a complete set of n-mers.

The '134 patent teaches that these "severe drawbacks" can be avoided by limiting the number of probes in the array in either of two ways: by using n-mers of only of about 4-6 nucleotides in length, or by using less than a complete set of n-mers. As indicated in the quotations above, the '134 patent explicitly advocates use of fewer than all probes. The '134 patent indicates that only n-mers of 5-6 nucleotides have been used successfully. *See* '134 Patent, col. 12, lines 21-23. The '134 patent illustrates only the use of 4-6 nucleotide n-mers. *See* '134 Patent, col. 6, lines 9-13; Examples 2, 10 and 13. The '134 patent goes on to teach that customized probes (and not a complete set of n-mers) are "structurally useful for identifying and binding to only those sequences which are homologous to the overhangs." Col. 10, lines 24-25, *see also*, col. 10, lines 11- 67. Such teachings would discourage one of skill in the art from using a complete set of n-mers and from using n-mers of about eight nucleotides of longer. Additionally, the passages cited above show that the '134 patent expressly teaches that one of skill in the art would not have a reasonable expectation of successfully using a microarray with a complete set of n-mers eight nucleotides or longer. Accordingly, the '134 patent does not disclose or teach the present invention.

The Examiner has also cited the '134 patent at col. 12, lines 9-19, discussing how many probes are needed to represent all n-mers of a given length. However, this passage merely mentions that an array of 4^n probes is needed in principle to represent all 4^n possible overhangs of length n. This passage does not advocate or enable use of all 4^n overhangs. Instead, it merely advocates use of a double-stranded region with a 3'-overhang. Therefore, at best, this passage is merely an invitation to experiment. However, it is irrelevent whether or not it may have been "obvious to experiment" because an "obvious to experiment" is not a proper standard for obviousness. *In re Dow Chemical Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

Applicant submits that the technology necessary for generating arrays containing complete sets of n-mers longer than 5-6 nucleotides only became available when applicant developed the ability to make microarrays. As evidenced by the teachings of the '134 patent, numerous problems and drawbacks existed that had to be overcome in order for complete sets of n-mers to be a workable solution. See, '134 Patent, col. 2, line 37 to col. 3, line 22 (listing six drawbacks realted to use of a complete set of n-mers.) Accordingly, the claimed invention is non-obvious in view of the '134 patent.

The Examiner admits that '134 patent does not teach hybridizing a reference polynucleotide to a second array and determining the presence of a mutation by comparing the reference and target hybridization patterns. Office Action at 3 (Sep. 18, 2001). However, according to the Examiner, such a comparison is disclosed in U.S. Patent 5,700,637 to Southern (the '637 patent'). Applicant submits that the '637 patent suffers from the same deficiencies as the '134 patent, providing mere speculation that a complete set of n-mers may be utilzed in a hybridization method employing a microarray.

According to the Examiner, the '637 patent teaches a method for determining the presence of a mutation in a target polynucleotide by hybridizing a target polynucleotide to a one array stripe and a reference polynucleotide to a second array stripe and determining the presence of a mutation by comparing reference and target hybridization patterns without sequencing the target polynucleotide. The Examiner cites the '637 patent at column 7, lines 10-31, at column 3, lines 58-62, at column 10, line 57 to column 11, line 4 as evidence allegedly supporting this position. Applicant submits that such "array stripes" are not microarrays.

Moreover, like the '134 patent, the '637 patent teaches that use of a complete set of n-mers is problematic. For example, the '637 patent provides a table at column 5 illustrating the size of the array matrix and how many sheets of film must be used. According to this table, one side of a matrix would be 100 mm and one piece of film would be needed if the length of the oligonucleotide or n-mer were 10 nucleotides. Such a matrix array is not a "microarray."

The '637 patent admits that automatic equipment for applying precursors needed for forming the matrix array has yet to be developed. See, '637 Patent, column 6, lines 35-36. The '637 patent provides speculation that it might be possible to resolve the "spots" of the matrix into smaller, better resolved arrays. Applicant submits that such speculation merely serves as an invitation to experiment and that whether or not is was "obvious to try" to make the present

invention, such is not the standard by which obviousness is assessed. *In re Dow Chemical Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

Moreover, the teachings of the '637 patent would not provide a reasonable expectation of successfully employing microarrays as claimed in the present application. For example, in Example 3, a length of 1 mm outer diameter silicon tubing was glued or clamped onto a microscope slide in the form of a "U" to create separate cavities where different probes could be made or attached. Such a method is not a viable method for making a microarray.

Applicant submits that the '637 patent does nothing to correct the defects of the '134 patent and, accordingly, the combination of the the '134 patent and the '637 patent does not disclose or teach the present invention.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 18th day of March 2002.

Anne M. Richards
Name

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Signature